SERUM CHOLESTEROL AND CANCER IN THE NHANES I EPIDEMIOLOGIC FOLLOWUP STUDY

ARTHUR SCHATZKIN ROBERT N. HOOVER
PHILIP R. TAYLOR REGINA G. ZIEGLER
CHRISTINE L. CARTER[1] DAVID B. LARSON
LISA M. LICITRA

Cancer Prevention Studies Branch, Division of Cancer Prevention and Control, and Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland 20892; Biometry and Clinical Applications Branch, Division of Biometry and Applied Sciences, National Institute of Mental Health, Rockville, Maryland 20897; and Information Management Services, Silver Spring, Maryland 20910, USA

Summary The relation between total serum cholesterol and cancer incidence and mortality was studied in a cohort based on a probability sample of the United States population. 5125 men (yielding 459 incident cancers and 258 cancer deaths) and 7363 women (398 cases, 186 deaths) were initially examined in 1971–75 and followed up for a median of 10 years. Men in the lowest cholesterol quintile had nearly double the risk of those in the highest quintile for both incidence and mortality. Among women a similar relation was seen for cancer mortality, but cancer incidence in the lowest quintile was only 1·2 times that of women in the highest quintile. The inverse cholesterol-cancer relation in men was present for cholesterol determinations made 6 or more years before diagnosis of cancer. It may be premature to dismiss the inverse relation between serum cholesterol and cancer simply as a preclinical marker of disease.

Introduction

SEVERAL cohort studies have shown an inverse relation between serum cholesterol and all cancer,[1-16] whereas others have demonstrated no such association.[17-25] The inverse relation, noted in a few investigations to be confined to cancers diagnosed in the first few years after cholesterol measurement, has been attributed to a possible cholesterol-lowering action of preclinical cancer.[3,13,14,16] Some studies, however, have found that the inverse relation did not disappear for malignancies diagnosed two or even more years after cholesterol determination.[4,8,9,11,12] A positive association between cholesterol and cancer at one major site has also been described.[26]

We report here the findings of a study of the relation between serum cholesterol and all cancer in a unique cohort based on a probability sample of the United States population.

Methods

The Cohort

The NHANES I Epidemiologic Followup Study (NHEFS) is a cohort study based on the National Health and Nutrition Examination Survey (NHANES I).[27] NHANES I was conducted by the National Center for Health Statistics from 1971 to 1975 on a probability sample of the civilian non-institutionalised population of the United States.[28] Tracing and re-interview for the NHEFS were done between 1981 and 1984. 14 407 adults aged 25–74 who were examined in 1971–75 were eligible for inclusion in the NHEFS. The mean ages at baseline were 52 for men and 48 for women. 33% of the men and 27% of the women were aged over 65 at entry into the study. 94% of the 5811 men and 92% of the 8596 women examined in NHANES I were successfully traced.

Identification of Cases

A cohort member was classified as a cancer case if there was any diagnosis of cancer (International Classification of Diseases codes 140–208, excluding non-melanoma skin cancer, ICD code 173) on a hospital record or death certificate. For cases identified through hospital records, the date of first admission with cancer listed in the discharge diagnosis was regarded as the incidence date. The date of death was considered as the incidence date for those cases for which only death certificate data were available. In the mortality analyses, only cancer listed as the underlying cause of death was considered to be a case.

Measurement of Cholesterol and Other Covariates

Cholesterol was determined from non-fasting baseline blood specimens with a semi-automated modified ferric-sulphuric method in the lipid laboratory of the Centers for Disease Control.[29,30]

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TABLE I—PERCENTAGES OF SUBJECTS HAVING VARIOUS CANCER RISK FACTORS WITHIN CHOLESTEROL QUINTILES*

Men	Serum cholesterol quintiles (mg/100 ml)					Women	Serum cholesterol quintiles (mg/100 ml)				
	≤182	183–205	206–226	227–254	≥255		≤179	180–203	204–229	230–261	≥262
Age ≥65 yr	27	33	30	36	38	Age ≥65 yr	9	11	23	33	47
Education <12 yr	49	49	47	49	48	Education <12 yr	42	39	41	43	44
PIR <1·69†	34	31	29	33	30	PIR <1·51†	35	33	33	33	30
BMI ≥27‡	28	30	34	37	40	BMI ≥27‡	27	31	34	37	40
Smoking ≥27 pack-yr‡	32	35	35	33	37	Smoking ≥13 pack-yr	19	19	19	22	23
Alcohol ≥5 g/day§	22	22	24	24	24	Alcohol ≥5 g/day§	13	15	14	15	15
Fat intake ≥41% kcal‡	32	34	33	37	32	Fat intake ≥40% kcal‡	31	34	35	36	36
Fibre intake <7·1 g/day†	32	31	32	33	35	Fibre intake <5·6 g/day†	29	33	33	35	36

BMI = body mass index. PIR = poverty index ratio.
*Percentages for all risk factors except age are age-adjusted by the direct method.[31] PIR is based on household income adjusted for family size and other demographic characteristics; ratios of 1·0, <1·0, and >1·0 indicate, respectively, "poverty level", "below poverty", and "above poverty". The fibre variable represents total dietary fibre.
†Lowest tertile. ‡Highest tertile. §Highest tertile among drinkers.

Data on age, education, poverty index ratio, body mass index, alcohol consumption, and diet were taken from the baseline interview. The dietary data were derived from a 24 h recall interview.[31,32] Smoking information was collected on only about half the subjects in NHANES I. For the rest, we inferred smoking status at baseline from questionnaire data obtained at follow-up from subjects or their next of kin.

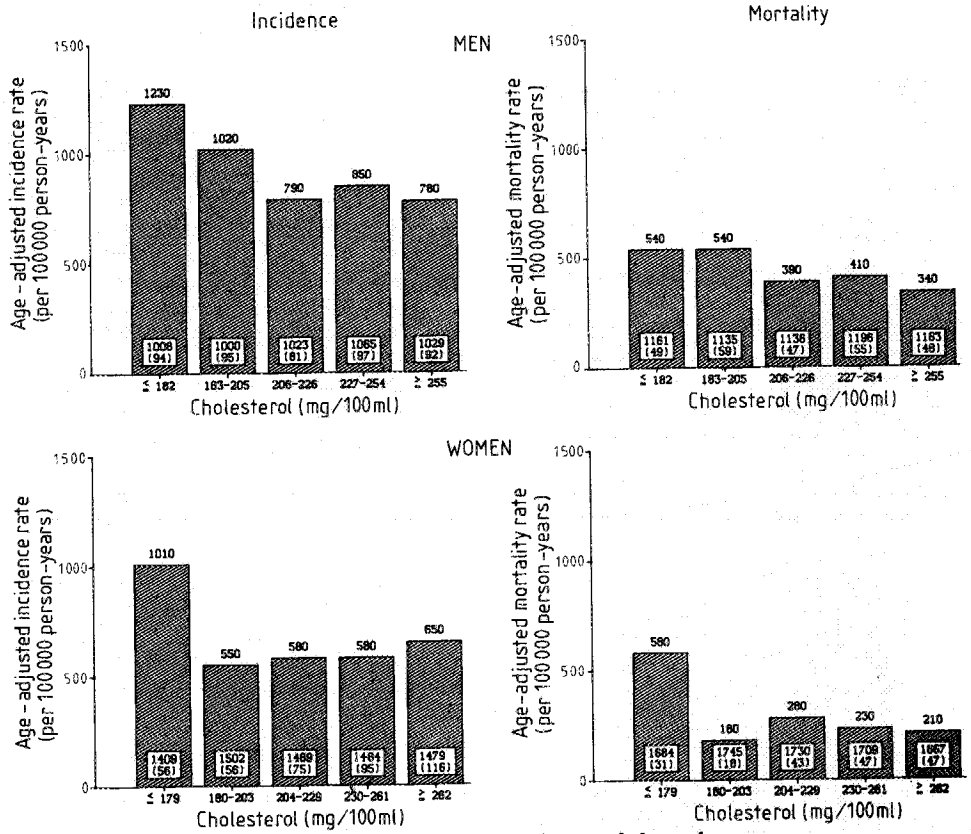
Populations for Incidence and Mortality Analyses

686 men and 1233 women were excluded from the incidence analyses. 351 eligible men and 675 eligible women could not be traced. 309 men and 483 women were traced alive but did not have a follow-up interview, either because they refused or because they could not be contacted. 20 men and 61 women were missing baseline serum cholesterol information. 10 men and 25 women with cancer of any site (except non-melanoma skin cancer) at baseline were excluded. A small number of men and women fell into more than one of these exclusion categories. Only those missing baseline serum cholesterol and/or those with cancer were excluded from the mortality analyses.

5125 men and 7363 women were included in the incidence analyses. 459 cancers were identified in men and 398 in women. 5791 men and 8535 women were included in the mortality analyses, and these included 258 men and 186 women who died of cancer. The median cohort follow-up time for all analyses was 10 years.

Analytical Procedures

Crude incidence (and mortality) rates for quintiles of serum cholesterol were calculated by dividing the number of new (and fatal) cancers occurring among subjects in that quintile by the total



Age-adjusted cancer incidence and mortality rates by level of serum cholesterol.

Rates are age-adjusted by the direct method[31] according to the age distribution of the NHEFS cohort. The numbers in each box refer to the numbers of subjects (cases) within each cholesterol level.

TABLE II—RELATIVE RISK ESTIMATES FOR ALL CANCER BY SERUM CHOLESTEROL LEVEL

	Incidence					Mortality				
	Cholesterol (mg/100 ml)					Cholesterol (mg/100 ml)				
	⩽182	183–205	206–226	227–254	⩾255	⩽182	183–205	206–226	227–254	⩾255
Men:										
RR*	1·6	1·3	1·0	1·1	(1·0)	1·6	1·6	1·1	1·2	(1·0)
95% CI	(1·2–2·1)	(1·0–1·9)	(0·7–1·3)	(0·8–1·4)	..	(1·0–2·3)	(1·1–2·3)	(0·7–1·7)	(0·6–1·7)	..
Multivariate RR†	1·7	1·5	1·0	1·2	(1·0)	1·9	1·9	1·4	1·4	(1·0)
95% CI	(1·2–2·6)	(1·0–2·2)	(0·7–1·5)	(0·8–1·8)	..	(1·0–3·4)	(1·1–3·4)	(0·8–2·5)	(0·8–2·5)	..
	⩽179	180–203	204–229	230–261	⩾262	⩽179	180–203	204–229	203–261	⩾262
Women:										
RR*	1·4	1·0	1·0	1·0	(1·0)	2·6	1·0	1·5	1·2	(1·0)
95% CI	(1·0–2·0)	(0·7–1·4)	(0·7–1·3)	(0·8–1·3)	..	(1·6–4·1)	(0·6–4·1)	(1·0–2·3)	(0·8–1·9)	..
Multivariate RR‡	1·2	1·0	0·8	0·9	(1·0)	2·0	1·0	1·2	1·2	(1·0)
95% CI	(0·8–1·9)	(0·7–1·5)	(0·6–1·2)	(0·6–1·2)	..	(1·0–3·8)	(0·5–2·1)	(0·7–2·2)	(0·7–2·0)	..

RR = relative risk. (1·0) indicates reference value.
*Age-adjusted in proportional hazards model that included variables for age and cholesterol.
†Model includes variables for age, education, body mass index, smoking (pack-years), alcohol, dietary fat as a percentage of total calories, dietary fibre, and cholesterol. Because some subjects were missing information on smoking (even when follow-up data were used) and/or diet, the number of cases in the multivariate models for incidence and mortality were reduced, respectively, to 257 and 127.
‡Model includes variables for age, education, body mass index, smoking (pack-years), alcohol, dietary fat as a percentage of total calories, dietary fibre, age at birth of first child, age at menarche, parity, and cholesterol. Because some subjects were missing information on smoking (even when follow-up data were used) and/or diet, the number of cases in the multivariate models for incidence and mortality were reduced, respectively, to 268 and 107.

number of person-years contributed by the subjects within that quintile. The number of person-years contributed by an individual subject was calculated from baseline to the time of cancer diagnosis or death or the time of the follow-up interview, whichever came first. Age-adjusted rates were calculated by the direct method.[33] Cox's proportional hazards regression technique was used to analyse the simultaneous relation of serum cholesterol, age, and other variables to cancer incidence and mortality in the cohort.[34,35]

Results

Mean total serum cholesterol (SD) was 221 (47) mg/100 ml for men and 222 (50) mg/100 ml for women. For men, the ratio of observed cancer cases to expected cases (based on age-specific, sex-specific, and race-specific incidence rates from the Connecticut Tumor Registry) was 1·04 (95% confidence interval, 0·95–1·14). The observed/expected ratio for women was 1·01 (0·91–1·11).

The relation of baseline total serum cholesterol to several potential cancer risk factors is shown in table I. In men baseline serum cholesterol varied directly with age, poverty index ratio, body mass index, and cigarette smoking. Little or no relation was observed between serum cholesterol and education or consumption of alcohol, fat (as a percentage of total calories), or fibre. Similar relations are seen in women, except that women with higher levels of cholesterol consumed more fat and less fibre.

Age-adjusted cancer incidence and mortality rates by quintiles of baseline cholesterol are shown in the figure. In men there was a consistent inverse relation between cholesterol and cancer rate for incidence and mortality. In women the inverse relation for mortality was stronger than that for incidence (both associations being determined largely by the elevated rate within the lowest cholesterol quintile). Inverse associations were confined to leukaemia and cancers of the lung, bladder, and pancreas in both men and women and to cancer of the cervix in women.

Age-adjusted and multivariate relative risk estimates from proportional hazards regression models are shown in table II. There was an inverse association between cholesterol and cancer incidence in men; the multivariate relative risk estimates (and 95% confidence intervals) for the first to fourth quintiles of cholesterol inclusive (in comparison with the highest quintile) were, respectively, 1·7 (1·2–2·6), 1·5 (1·0–2·2), 1·0 (0·7–1·5), and 1·2 (0·8–1·8). The trend test for incidence was significant ($\chi^2 = 9·77$, $p = 0·002$). Similar results were obtained when incident cases reported by death certificate only were eliminated and when mortality was analysed.

For incidence in women there was a small non-significant increase in risk confined to the lowest quintile of cholesterol (table II). The multivariate relative risk estimates for incidence in women were 1·2 (0·8–1·9), 1·0 (0·7–1·5), 0·8 (0·6–1·2), 0·9 (0·6–1·2). The trend test for incidence was not significant ($\chi^2 = 2·34$, $p = 0·13$). Negligible differences

TABLE III—RELATIVE RISK OF CANCER IN RELATION TO SERUM CHOLESTEROL LEVEL, BY YEARS OF FOLLOW-UP

	Relative risk (men)*				Relative risk (women)*		
—	0–1·9 yr (n = 56)	2–5·9 yr (n = 134)	6+ yr (n = 168)	—	0–1·9 yr (n = 58)	2–5·9 yr (n = 125)	6+ yr (n = 153)
Serum cholesterol (mg/100 ml):				*Serum cholesterol (mg/100 ml):*			
< 182	0·8 (0·3–1·9)	1·5 (0·9–2·5)	2·2 (1·3–3·7)	⩽179	3·3 (1·3–8·2)	0·6 (0·3–1·3)	1·0 (0·6–1·8)
183–205	1·3 (0·6–2·6)	1·0 (0·6–1·7)	1·8 (1·1–3·1)	180–203	1·3 (0·4–3·8)	1·0 (0·6–1·8)	0·8 (0·5–1·4)
206–226	0·6 (0·2–1·4)	0·9 (0·6–1·6)	1·7 (1·0–2·9)	204–229	2·8 (1·5–5·9)	0·8 (0·5–1·3)	0·7 (0·4–1·2)
227–254	0·8 (0·4–1·7)	0·8 (0·7–2·0)	1·8 (1·1–3·0)	230–261	1·9 (0·9–4·0)	0·6 (0·4–1·0)	1·0 (0·7–1·5)
⩾255	(1·0) ..	(1·0) ..	(1·0) ..	⩾262	(1·0) ..	(1·0) ..	(1·0) ..

n = number of cases confirmed by hospital records.
*Age-adjusted RR (and 95% CI) derived from follow-up time-specific proportional hazards models that included variables for age and cholesterol. Estimates were not materially altered in multivariate models that included variables for age, serum cholesterol, education, body mass index, smoking (pack-years), alcohol, dietary fat as a percentage of total calories, dietary fibre, and, for women, age at birth of first child, age at menarche, parity, and serum cholesterol.

resulted from the elimination of those incident cases identified from death certificate only. The risk was elevated for women in the lowest cholesterol quintile in the analysis of mortality (RR = 1·9, 1·0–3·4).

The relation of cholesterol to cancer incidence and mortality was similar across subgroups of various cancer risk factors, including age, education, body mass index, smoking, alcohol consumption, and fat consumption. In women the inverse cholesterol-cancer relation for both incidence and mortality was observed only in those aged under 50.

We examined the cholesterol-cancer relation for three distinct follow-up periods—under 2, 2–5, and 6 or more years from the time of cholesterol measurement to cancer diagnosis (table III). Only those incident cases confirmed by hospital records were analysed, since the time of cancer diagnosis was thought to be less reliable for cases identified by death certificate only. Among men the inverse relation was strongest for cases diagnosed 6 or more years after serum cholesterol was measured. There was a statistically significant excess risk only among women in the lowest cholesterol quintile in whom cancer was diagnosed within 2 years of cholesterol determination.

Discussion

In this cohort study based on a probability sample of the US population, an inverse relation was observed between total serum cholesterol and cancer incidence and mortality among men. A majority of earlier cohort studies have reported similar findings,[1-16] although some have found no association between cholesterol and cancer in men.[17-20,22-25]

In order to investigate the "preclinical cancer effect" (reverse causation) hypothesis, we analysed the relation between cholesterol and cancer according to the interval between cholesterol measurement and cancer diagnosis. We found that the inverse relation between cholesterol and cancer in men did not diminish with increasing time to diagnosis and was, in fact, strongest for cancers diagnosed 6 or more years after cholesterol determination. These findings do not support the preclinical cancer effect explanation for the inverse cholesterol-cancer relation in men. However, our knowledge of the natural history of cancer is insufficient to dismiss completely the possibility that the carcinogenic process could affect cholesterol metabolism many years before a tumour becomes clinically apparent.

In the few previous studies of the relation between cholesterol and cancer in women, no significant association has been found,[9,12,13,15,18,24,25] although trends towards both an inverse[9,12,15] and a direct[13] relation have been observed. Our data showed a non-significant inverse relation for cancer incidence among women in the lowest cholesterol quintile. For mortality, a significant inverse association for women was observed in the lowest quintile. These data suggest an inverse relation in women that was largely limited to more lethal cancers. We note that the site-specific cancers among which inverse cholesterol-cancer relations were found comprised a greater proportion of total cancers in men than in women.

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Correspondence should be addressed to A. S., National Institutes of Health, National Cancer Institute, Blair Building, Room 6A-01, Bethesda, MD 20892, USA.

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